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Epigenetic Regulation of Male Fate Commitment from an Initially Bipotential System

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ABSTRACT

A fundamental goal in biology is to understand how distinct cell types containing the same genetic information arise from a single stem cell throughout development. Sex determination is a key developmental process that requires a unidirectional commitment of an initially bipotential gonad towards either the male or female fate. This makes sex determination a unique model to study cell fate commitment and differentiation *in vivo.* We have focused this review on the accumulating evidence that epigenetic mechanisms contribute to the bipotential state of the fetal gonad and to the regulation of chromatin accessibility during and immediately downstream of the primary sex-determining switch that establishes the male fate.

1. INTRODUCTION

Vertebrates share a common template to achieve development of two distinct sexes. Initially, male and female embryos are indistinguishable. During development, the embryonic gonad forms with the unique ability to differentiate into two alternative organs: testes (males) or ovaries (females) (Fig. 1A). Gonadal differentiation diverges based on a genetic or environmental switch that activates one pathway and represses the other. This system presents an interesting model to explore the various levels of regulation involved in fate commitment of single cells and the coordination of the entire cell community that makes up the bipotential gonad.

One interesting characteristic of vertebrate sex determination is the plastic ability to switch between a male and female fate. For example, in most reptilian species, the incubation temperature of the egg controls the sex of the offspring, and switching eggs between temperatures during a critical window of development results in a switch to the opposite sex. Many fish can undergo sex reversal as adults, and although mammals do not undergo full sex reversal, the removal of certain key transcription factors can cause a switch in the identity of female cells to male cells (Ottolenghi et al., 2007, Uhlenhaut et al., 2009) or male cells to female cells (Matson et al., 2011). Importantly, gonadal cells do not switch randomly to another fate, but specifically to their developmental alternative fate.

Although multiple mechanisms are interwoven in the process of fate commitment and canalization as one sex or the other, epigenetic regulation is emerging as an important component. Epigenetics, the study of changes to gene function without changes in the DNA sequence, is capable of imposing a stable differentiation state throughout cell division. Between 1940 and 1956, Conrad Waddington proposed the concept of an epigenetic landscape to describe the process of cell fate commitment during development. He envisioned that